

# Palliative radiation for bone metastases from hepatocellular carcinoma: practice patterns and the amount of remaining life spent receiving treatment

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**Background:** Palliative radiation therapy (RT) for bone metastases (BMs) is a common practice. Wide variation exists in clinically used dose schema despite numerous studies demonstrating palliative equipoise between single and multifraction courses. We hypothesize that fraction scheme for palliating BMs for hepatocellular carcinoma (HCC) significantly affects how patients spend their remaining time.

**Methods:** Patients with osseous HCC metastases who received RT were identified from the National Cancer Database (2004–2013). The percentage of remaining life spent receiving radiation therapy (PRLSRT) and the number of incomplete RT courses were calculated. Kaplan-Meier analysis and Cox proportional hazards models were used to evaluate trends and predictors.

**Results:** A total of 1,331 patients met the inclusion criteria. Median overall survival (OS) was 3.3 months. Just 49 (3.7%) of patients received single fraction RT and 34% received >10 fractions. The mean and median PRLSRT were as follows: 1 fraction (8.9% and 3.0%), 2–5 fractions (32.9% and 24.3%), 6–10 fractions (27.2% and 15.9%), and >10 fractions (24.1% and 14.4%). Of the patients with PRLSRT >50%, 99.6% received multifraction RT. The proportion of incomplete RT courses increased as fraction size decreased from 17.6% with 4 Gy to 34% with 2 Gy.

**Conclusions:** Single fraction palliative RT is vastly underutilized despite no additional palliative benefit with multifraction RT. PRLSRT significantly increased with multifraction RT. In the palliative treatment of painful BMs from HCC, single fraction treatment reduces time spent receiving radiation treatments and maximizes the number of patients who complete the prescribed treatment.

**Keywords:** Palliative radiation therapy; bone metastases (BMs); hepatocellular carcinoma (HCC)

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## 1 Introduction

2 As advances in cancer treatment prolong survival, bone  
3 metastases (BMs) from underlying malignancy are  
4 becoming an increasingly prevalent source of pain leading  
5 to significant deterioration in quality of life (1-4). Bone  
6 pain is a leading cause of morbidity in patients with cancer,  
7 and BMs represent the leading cause for bone pain (3).  
8 Complications from BMs include hypercalcemia, decreased  
9 function and quality of life, pathological fractures, as  
10 well as neurovascular compression (3,5). Indications for  
11 the treatment of BMs include pain, skeletal functional  
12 impairment, as well as pathological fractures (5).

14 The diagnosis of hepatocellular carcinoma (HCC)  
15 confers a poor prognosis with a 5-year survival of 31% for  
16 those with localized disease and 2% for metastatic disease (6).  
17 Most patients are diagnosed at advanced stages and receive  
18 palliative treatments (7). BMs in HCC are estimated at  
19 6–33%, however a more recent study has estimated as  
20 high as 32.9% with annual incidence of 6.4% (8,9). RT  
21 is an effective means for the palliation of pain caused by  
22 BMs with rates of pain relief as high as 79% (10-12). Many  
23 studies investigating fractionation schemes of RT for  
24 palliation of BMs have demonstrated no difference in pain  
25 outcomes, the development of spinal cord compression,  
26 or pathologic fracture between those treated with single  
27 or hypofractionated treatments versus more protracted  
28 radiation courses (13-20). Despite this data there remain a  
29 wide number of treatment regimens in use. Current ASTRO  
30 approved dose-fractionation schema include: 8 Gy/1 Fx,  
31 20 Gy/5 Fx, 24 Gy/6 fx and 30 Gy/10 fx (21). A Choosing  
32 Wisely recommendation posits that single fraction RT  
33 should be used for all uncomplicated BMs (22).

34 The purpose of this study was to investigate practice  
35 patterns in patients treated with palliative RT for BMs from  
36 HCC. The hypothesis is that patients undergoing long-  
37 course palliative regimens spend a greater portion of their  
38 remaining life receiving radiation treatments and higher  
39 rates of incomplete courses compared to those receiving  
40 single fraction treatments. Due to the poor prognosis of  
41 HCC, maximizing quality of life and minimizing travel and  
42 time receiving RT should be of the utmost importance.  
43 Spending a significant portion of one's remaining time  
44 receiving daily palliative radiation treatments may detract  
45 from the anticipated benefit of the radiation and patient  
46 overall quality of life.

47 We present the following article in accordance with the  
48 STROBE reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-21-2657/rc>).

## Methods

### Study design

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The National Cancer Database (NCDB) was queried to identify patients with HCC metastases to the bone who received RT using International Classification of Diseases-Third revision (ICD-3) histology codes 8170-8175 and the codes for radiation treatment volume for bone (24–28, 37, 38, and 40) between 2004 and 2013. Patients with missing or unknown radiation dose data, and lacking follow-up were excluded. The duration of time spent receiving radiation treatment was identified and used to calculate percentage of remaining life spent receiving radiation therapy (PRLSRT):

$$\text{PRLSRT}(\%) = 100 \frac{\text{Elapsed days of RT}}{\text{Elapsed days from start of RT to death}} \quad [1]$$

An exploratory analysis was performed to determine the hypothetical percentage of remaining life spent receiving radiation therapy ( $H_{\text{PRLSRT}}$ ) had the patients in the multifraction subset received single fraction RT instead:

$$H_{\text{PRLSRT}}(\%) = 100 \frac{\text{Hypothetical single day of RT}}{\text{Elapsed days from start of RT to death}} \quad [2]$$

Finally, we calculated the radiation therapy-free life gained (RTFLG), representing the percentage of a patient's life which could have been spent outside of the hospital setting had they instead received single fraction RT:

$$\text{RTFLG}(\%) = \frac{\text{Elapsed days of RT} - \text{Hypothetical single day of RT}}{\text{Elapsed days from start of RT to death}} \quad [3]$$

$$= \text{PRLSRT} - H_{\text{PRLSRT}}$$

Descriptive analysis of practice patterns including most common dose-fractionation schemes, sites of metastasis and various other demographic and patient related characteristics were performed. To calculate the number of incomplete RT courses, dose per fraction was calculated and compared to standard dose regimens: 4 Gy/fraction (20–24 Gy in 5–6 fractions), 3 Gy/fraction (30 Gy in 10 fractions), 2.5 Gy/fractions (35–37.5 Gy in 14–15 fractions), and 2 Gy/fraction (40 Gy in 20 fractions). Patients with a standard fraction size as defined above, but less than the appropriate number of fractions for a standard regimen we deemed to have an incomplete course. For most analysis, patients were stratified into four treatment groups based on number of fractions received: 1, 2–5, 6–10, and greater than 10.

### 99 *Statistical analysis*

100 Univariate comparisons were made using Chi-Square,  
 101 ANOVA, or *t*-tests. Kaplan-Meier Curves and log-  
 102 rank test were used to examine survival outcomes and  
 103 Cox proportional hazards models were used to identify  
 104 predictors of survival. Overall survival (OS) was calculated  
 105 from the start of RT until death or last follow-up.  
 106 Hazards ratio (HR), and 95% confidence intervals (CIs)  
 107 were reported for the Cox regression analysis. Alpha was  
 108 established at 0.05 for all tests and  $P < 0.05$  was considered  
 109 significant. Statistical analyses were performed using SPSS  
 110 version 24.0 (IBM Corp., New York, NY, USA).

### 113 **Results**

114 A total of 1,331 patients received palliative RT for BMs  
 115 from HCC. For the entire cohort, median patient age was  
 116 61 years. The vast majority of patients were male (86.3%)  
 117 and Caucasian (74.9%). Patient characteristics of the entire  
 118 cohort as well as subdivided by fractionation group (1 Fx,  
 119 2–5 Fx, 6–10 Fx, >10 Fx) are outlined in *Table 1*. Most  
 120 common sites of treatment were the spine (62.3%), hip/  
 121 pelvis (18.5%), and shoulder/extremity (10.5%). Most  
 122 patients received 30 Gy in 10 fractions (36.3%). The ten  
 123 most common dose-fraction schemes are shown in *Figure*  
 124 *1A* and annual usage trends for RT separated by fraction  
 125 group are shown in *Figure 1B*. Over time there appeared  
 126 to be a trend, albeit small, toward decreased utilization  
 127 of longer (>10 fx) multifraction regimens and increased  
 128 utilization of single fraction and hypofractionated (defined  
 129 as 5 or fewer fractions) regimens. Peak annual usage of  
 130 single fraction palliative RT was 5.5%. Survival after  
 131 radiation within this cohort was very poor with median  
 132 OS, **1- and 2-year OS of 3.3 months, 17.3% and 7.8%,**  
 133 **respectively.** Survival plots for the entire cohort as well as  
 134 stratified by fraction group are shown in *Figure 2*. Following  
 135 the start of RT, 21%, 45.8% and 66.6% of patients died  
 136 within 1, 3 and 6 months, respectively.

137  
 138 Forty-nine (3.7%) patients received single fraction  
 139 palliative RT compared to 198 (14.9%), 628 (47.2%), and  
 140 456 (34.3%) of patients who received 2–5, 6–10, and >10 Fx,  
 141 respectively. Of those who received a single treatment 24  
 142 patients (50% of single fractions cohort and 1.8% of the  
 143 entire cohort) were treated with stereotactic radiosurgery.  
 144 Overall mean and median PRLSRT were 26.4% and  
 145 15.4%, respectively. Mean and median PRLSRT were 8.9%  
 146 and 3.0% for 1 Fx, 32.9% and 24.3% for 2–5 Fx, 27.2%

and 15.9% for 6–10 Fx, and 24.1% and 14.4% for >10 Fx  
 (Table 2). Mean and median PRLSRT was significantly  
 different in all fraction groups when compared individually  
 to the single fraction group (all  $P < 0.001$ ). Distributions  
 of PRLSRT as a function of fraction group are shown in  
 Figures 3,4. The majority of patients had PRLSRT  $\leq 25\%$   
 regardless of fraction group. There were no patients in the  
 1Fx group who had PRLSRT  $> 75\%$ . Nearly all (248/249  
 or 99.6%) patients with a PRLSRT  $\geq 50\%$  received  
 multifraction regimens.

The percentage of patients with incomplete courses  
 increased as the dose per fraction decreased and the number  
 of fractions increased. The percent incomplete course was  
 17.6% for 4 Gy per fraction, 21.7% for 3 Gy/fraction,  
 24% for 2.5 Gy/fraction, and 34% for 2 Gy/fraction.  
 On multivariate analysis, increasing age, elevated AFP,  
 shorter number of radiation fractions, spine metastasis, not  
 receiving chemotherapy, and palliative RT less than 30 days  
 after diagnosis was associated with shorter survival (Table 3).

In our exploratory analysis, mean  $H_{\text{PRLSRT}}$  compared to  
 mean PRLSRT were 7.2% and 32.9% for 2–5 Fx, 2.2%  
 and 27.2% for 6–10 Fx, and 1.1% and 24.1% for >10 Fx  
 (Table 2) and was statistically significant for all groups  
 ( $P < 0.001$ ). Distributions of  $H_{\text{PRLSRT}}$  as a function of fraction  
 group are shown in Figure 4. For the subset of the cohort  
 receiving multiple fraction RT, the mean and median  
 RTFLG were 24.5% and 14.8%, respectively.

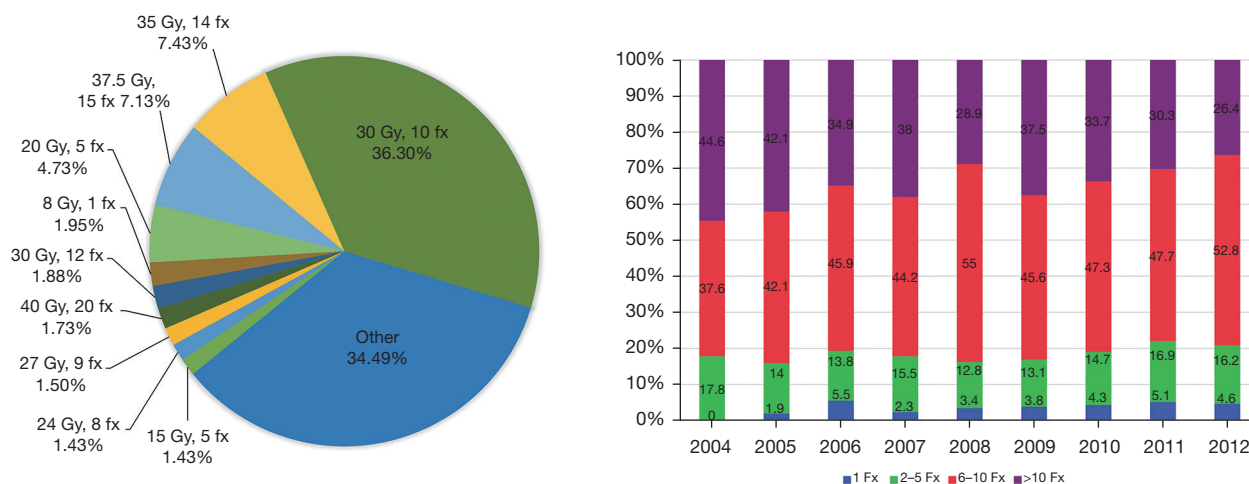
### Discussion

The diagnosis of HCC with BMs confers a grim prognosis.  
 Median survival in this cohort was 3.3 months with a  
 17.3% 1-year and a 7.8% 2-year OS. These findings  
 are consistent with the existing literature rates of 1- and  
 2-year OS of 18.1% and 6.3% reported by Choi *et al.* (23).  
 Given the short survival time and the equivalence of single  
 and multifraction regimens for the treatment of BMs,  
 efforts should be made to reduce palliative RT duration to  
 maximize patient comfort, quality of life and reduce time  
 spent receiving RT. Numerous studies have shown that there  
 is no difference in pain response rates, time to improvement  
 in pain, time to complete pain relief or duration of pain  
 relief when comparing single and multifraction palliative  
 RT for BMs (13-20,24). Despite those findings, this study  
 demonstrates a significant underutilization of single fraction  
 palliative RT in the treatment of BMs from HCC. Only  
 3.7% of patients received single fraction therapy, of which  
 about half received SRS (1.8% of total population), and a

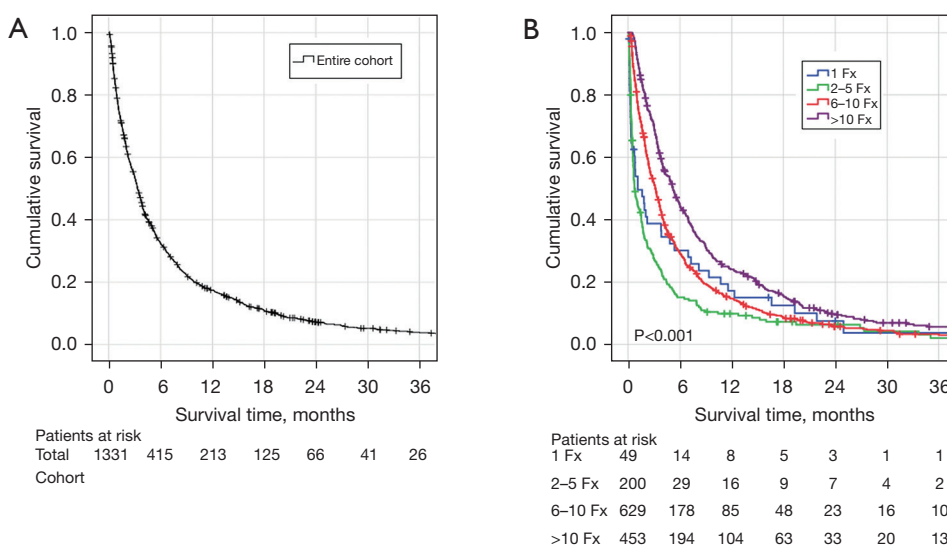
**Table 1** Patient characteristics

Variables	Total cohort (n=1,331) (%)	Division by fraction group				P value
		1 fraction n=49 (3.7%) (%)	2 to 5 fractions n=200 (15.0%) (%)	6 to 10 fractions n=629 (47.3%) (%)	>10 fractions n=453 (34.0%) (%)	
Age (years), median (range)	61 [20–90]	62 [44–86]	61 [45–89]	61 [20–90]	62 [30–89]	0.463
Median OS (months)	3.3	1.1	0.7	3.1	5.1	<0.001
Treatment location						
Rib/chest wall	89 (6.7)	2 (4.1)	16 (8.0)	37 (5.9)	34 (7.5)	0.002
Spine	830 (62.3)	27 (55.1)	135 (67.5)	419 (66.6)	249 (55.0)	
Hip/pelvis	246 (18.5)	8 (16.3)	30 (15.0)	99 (15.7)	109 (24.1)	
Shoulder/extremity	140 (10.5)	10 (20.4)	15 (7.5)	63 (10.0)	52 (11.5)	
Skull	26 (2.0)	2 (4.1)	4 (2.0)	11 (1.7)	9 (2.0)	
Gender (male)	1,149 (86.3)	41 (83.7)	174 (87.0)	534 (84.9)	400 (88.3)	0.378
Ethnicity						
Caucasian	998 (74.9)	36 (73.5)	155 (77.5)	455 (72.3)	352 (77.7)	0.251
African American	230 (17.3)	7 (14.3)	30 (15.0)	127 (20.2)	66 (14.6)	
Other	90 (6.8)	6 (12.2)	13 (6.5)	42 (6.7)	29 (6.4)	
Not specified	13 (1.0)	0 (0.0)	2 (1.0)	5 (0.8)	6 (1.3)	
Insurance						
Private	423 (31.8)	18 (36.7)	65 (32.5)	197 (31.3)	143 (31.6)	0.635
Government	778 (58.5)	25 (51.0)	116 (58.0)	362 (57.6)	275 (60.7)	
Uninsured	110 (8.3)	5 (10.2)	14 (7.0)	60 (9.5)	31 (6.8)	
Unknown	20 (1.5)	1 (2.0)	5 (2.5)	10 (1.6)	4 (0.9)	
Charlson-Deyo score						
0	781 (58.7)	29 (59.2)	111 (55.5)	359 (57.1)	282 (62.3)	0.095
1	304 (22.8)	11 (22.4)	51 (25.5)	161 (25.6)	81 (17.9)	
≥2	246 (18.5)	9 (18.4)	38 (19.0)	109 (17.3)	90 (19.9)	
Chemotherapy (none)	801 (60.2)	33 (67.3)	138 (69.0)	391 (62.2)	239 (52.8)	0.001
Treating facility (academic)	518 (38.9)	19 (38.8)	92 (46.0)	263 (41.8)	144 (31.8)	0.002
Diagnosis to RT start						
≤1 month	780 (58.6)	23 (46.9)	119 (59.5)	379 (60.3)	259 (57.2)	0.524
1 < months ≤3	414 (31.1)	20 (40.8)	56 (28.0)	190 (30.2)	148 (32.7)	
>3 months	137 (10.3)	6 (12.2)	25 (12.5)	60 (9.5)	46 (10.2)	
Income quartile						
<\$38,000	354 (26.6)	9 (18.4)	57 (28.5)	174 (27.7)	114 (25.2)	0.032
\$38,000–\$47,999	323 (24.2)	10 (20.4)	53 (26.5)	131 (20.8)	129 (28.5)	
\$48,000–\$62,999	310 (23.3)	20 (40.8)	39 (19.5)	149 (23.7)	102 (22.5)	
≥\$63,000	304 (22.8)	10 (20.4)	46 (23.0)	158 (25.1)	90 (19.9)	
Unknown	41 (3.1)	0 (0.0)	5 (2.5)	17 (2.7)	18 (4.0)	

OS, overall survival; RT, radiation therapy.



**Figure 1** Distribution of fractionation schemes and trends in utilization. (A) Ten most common dose-fractionation schemes; (B) annual utilization trends of palliative RT by fraction group. Gy, gray; Fx, fraction.



**Figure 2** Kaplan-Meier survival curves of overall survival. (A) The entire cohort and (B) stratified by fraction groups. Fx, fraction.

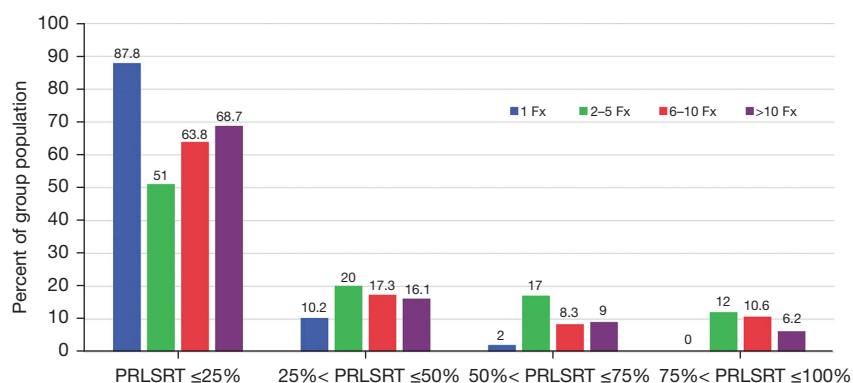
195 substantial 34% of patients received >10 Fx.  
 196 In this study the PRLSRT metric was used to  
 197 characterize how the choice of dose-fraction scheme affects  
 198 how patients spend their remaining life. Patients receiving  
 199 single fraction RT had a mean 8.9% PRLSRT, compared to  
 200 32.9%, 27.5%, and 24.1% for patients receiving 2-5, 5-10,  
 201 and >10 Fx, respectively. Patients receiving multifraction  
 202 RT spend a significantly higher proportion of their final  
 203 days receiving RT. Likewise, longer courses increase the  
 204 proportion of incomplete courses of RT. Approximately  
 205 one-third of patients prescribed multifraction regimens

206 did not complete their prescribed RT course, which could  
 207 suggest that the burden of time, energy, and resources  
 208 required to complete multifraction courses outweighed  
 209 the potential benefits of completing treatment for many  
 210 patients. This burden likewise potentially eroded the  
 211 anticipated benefits of palliative RT.  
 212 It was hypothesized that PRLSRT would increase  
 213 proportionally with number of fractions received, but  
 214 that trend was not observed in these data. The highest  
 215 PRLSRT corresponded to the 2-5 Fx group, which also  
 216 had the lowest median survival at 0.72 months while the

**Table 2** PRLSRT,  $H_{\text{PRLSRT}}$  and RTFLG metrics stratified by fraction group

Variables	Total cohort (n=1,331)	Division by fraction group			
		1 Fx n=49 (3.7%)	2–5 Fx (n=200) (15.0%)	6–10 Fx (n=629) (47.3%)	>10 Fx (n=453) (34.0%)
Mean PRLSRT (%)	26.4	8.9	32.9	27.2	24.1
Median PRLSRT (%)	15.4	3.0	24.3	15.9	14.4
Mean $H_{\text{PRLSRT}}$ (%)	2.59	N/A	7.2	2.2	1.1
Median $H_{\text{PRLSRT}}$ (%)	1.0	N/A	4.6	1.1	0.7
Mean RTFLG (%)	24.5	N/A	25.9	25.1	23.0
Median RTFLG (%)	14.8	N/A	20.1	14.8	13.8

PRLSRT, percentage of remaining life spent receiving radiation therapy.  $H_{\text{PRLSRT}}$ , hypothetical percentage of remaining life spent receiving radiation therapy RTFLG, radiation therapy-free life gained; N/A, not applicable.

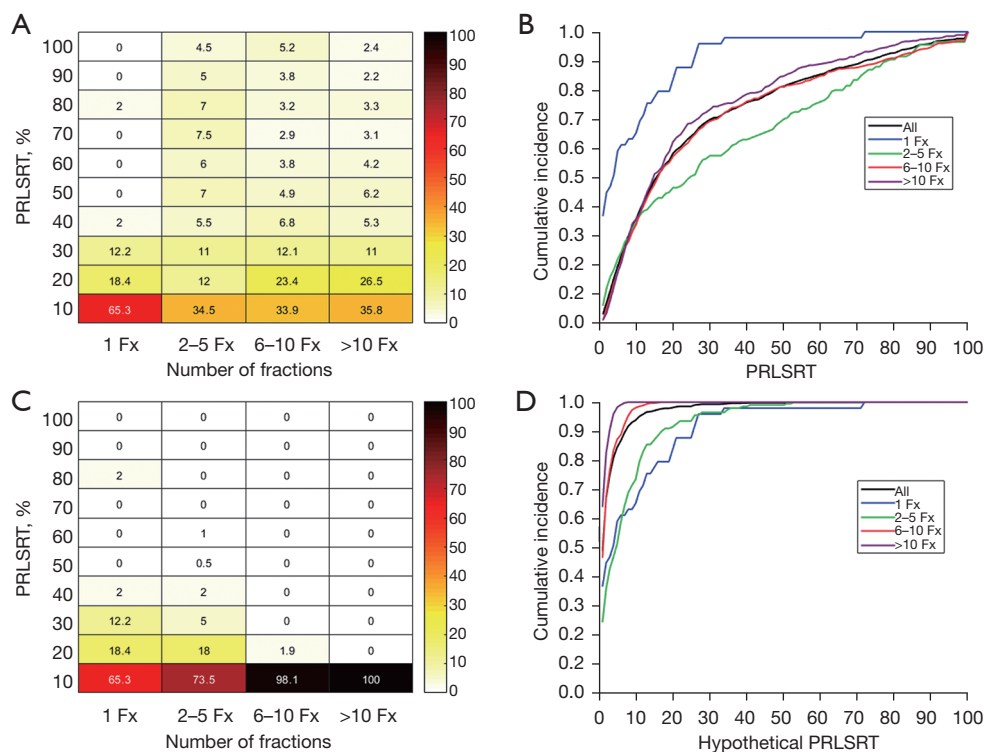


**Figure 3** Distribution of PRLSRT by fraction group and PRLSRT quartile. PRLSRT, percentage of remaining life spent receiving radiation therapy; Fx, fraction.

217 >10 Fx group had the highest median OS at 5.1 months.  
 218 It is possible that the increased PRLSRT observed in the  
 219 2–5 fraction group reflects both a consideration regarding  
 220 prognosis when selecting fractionation schema and a  
 221 possible reluctance for single fraction treatments. Instead of  
 222 receiving a single fraction, patients with the worse prognosis  
 223 were given a 2–5 fraction regimen because providers  
 224 may have been more comfortable and experienced with  
 225 these regimens, which resulted in a higher PRLSRT and  
 226 shorter survival in this group (25). Clinicians should choose  
 227 treatment regimens that reflect the patient's prognosis  
 228 and match the goals of treatment with the goals of care.  
 229 Given the poor survival in this cohort and in the literature,  
 230 increased consideration should be given to single fraction  
 231 palliative RT. If those in the 2–5, 6–10 and >10 Fx groups  
 232 had received just single fraction RT, without compromising  
 233 outcome the mean PRLSRT would have improved from

32.9%, 27.2%, and 24.1% to 7.2%, 2.2%, and 1.1%,  
 respectively. Patients also would have gained a mean 25.9%,  
 25.1%, and 23.0%, respectively, of their remaining life back  
 outside of the hospital setting.

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 There are a number of reasons why radiation oncologists  
 are reluctant to use single fraction regimens. The most  
 important of which is likely the higher reported retreatment  
 rate after single fraction treatment. Retreatment after single  
 fractions has been previously shown to be in upwards of  
 20–30% for single fraction RT compared to 7.4% in the  
 multiple fraction group with retreatment likelihood 3.44-  
 fold higher (95% CI: 2.67 to 4.43) (18,24,26). Time to  
 retreatment differs with average of 14 weeks (single fraction)  
 versus 23 weeks (multifraction) (27). Additionally the Bone  
 Pain Trial Working group reported retreatment probability  
 at 3 and 6 months was roughly 10% and 20% for single  
 fraction and 5% and 10% for multi-fraction treatments (24).



**Figure 4** Heat maps and cumulative PRLSRT graphs. (A) and (C) are heat map distributions of PRLSRT tertials by fraction group (A is actual distribution, C is the hypothetical PRLSRT distribution based on all patients receiving single fraction). Y-axis is the PRLSRT tertials, X-axis is the fraction groups. (B) and (D) are cumulative incidence graphs depicting PRLSRT distributions by fraction group (B is actual distribution, D is the hypothetical PRLSRT distribution). Y-axis is the cumulative incidence in percentages, X-axis is the PRLSRT percentage. PRLSRT, percentage of remaining life spent receiving radiation therapy; Fx, fraction.

251 However, there is no difference in time to first increase in  
 252 pain (24) and pain scores prior to retreatment were lower  
 253 or no different in the single fraction group (27). These  
 254 data suggest that physician bias and increased willingness  
 255 to give repeat treatment following single dose RT, rather  
 256 than actual necessity, explains reported differences in  
 257 retreatment rates (16,24,27). Determination regarding  
 258 radiation treatment schema should be considered within  
 259 the context of the underlying malignancy. Most patients  
 260 with HCC requiring RT for osseous metastases have a poor  
 261 overall poor prognosis and anticipated survival of only a few  
 262 months, so the retreatment rates are likely irrelevant since  
 263 most patients will not live long enough. Considering the  
 264 prognosis and time to retreatment should help reduce the  
 265 reluctance for using single fraction treatment in this cohort,  
 266 except for those small handful of patients with potential for  
 267 longer survival.

268 While most RT is given in the outpatient setting, it is  
 269 of utmost importance to consider the patient's wishes with

270 their remaining time and the socioeconomic implications of  
 271 RT when selecting the dose-fraction scheme. Multifraction  
 272 RT often requires daily trips to the radiation center that  
 273 may be a significant distance from home (18). This may  
 274 create a significant hardship, especially in patients with poor  
 275 performance status. Significant time, energy, strength, and  
 276 other resources are required from the patients and their  
 277 caregivers to complete multi-fraction regimens and often,  
 278 patients fail to complete the planned course of treatment.  
 279 The number of incomplete courses rose as the fractional  
 280 dose decreased and the number of treatments increased.  
 281 When RT courses are stopped early, the anticipated  
 282 palliative benefits may not be realized.

283 This study identifies several factors associated with  
 284 decreased survival for patients with HCC who received  
 285 palliative radiation for BMs: elevated AFP, spine *vs* non-  
 286 spine osseous metastasis, age, the use of chemotherapy, and  
 287 time from diagnosis to receiving palliative RT. Many of  
 288 these factors have also been reported by others (9,23,28-30).

**Table 3** Univariate and multivariate analysis of overall survival after palliative RT

Category	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	P value	Hazard ratio	95% confidence interval	P value
Age continuous variable	1.007	1.002–1.013	0.007	1.007	1.001–1.012	0.017
Sex [male (ref) vs. female]	1.091	0.924–1.288	0.305			
Charlson-Deyo Score						
0	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(ref)
1	1.161	1.011–1.333	0.034	1.092	0.948–1.259	0.222
2	1.119	0.960–1.303	0.150	1.132	0.969–1.322	0.119
Treating facility						
Academic	(Ref)	(Ref)	(Ref)			
Other	0.956	0.852–1.074	0.452			
Insurance status						
Private	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Government	1.132	0.999–1.284	0.052	0.100	0.964–1.255	0.156
Uninsured/unknown	1.237	0.992–1.542	0.058	1.092	0.874–1.368	0.435
Alpha-Feto protein						
Normal	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Elevated	1.337	1.098–1.627	0.004	1.282	1.050–1.565	0.015
Unknown	1.235	1.004–1.518	0.045	1.247	1.011–1.537	0.039
Number of fractions						
1 fraction	1.436	1.056–1.954	0.021	1.699	1.244–2.319	0.001
2–5 fractions	2.037	1.707–2.430	<0.001	2.039	1.700–2.446	<0.001
6–10 fractions	1.503	1.165–1.503	<0.001	1.299	1.141–1.478	<0.001
>10 fractions	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Months from diagnosis to RT						
≤30 days	1.378	1.131–1.679	0.001	1.286	1.052–1.572	0.014
>30 to ≤90 days	1.189	0.964–1.465	0.106	1.218	1.218–1.505	0.068
>90 days	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Osseous site						
Spine	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Other bone site	1.404	1.249–1.579	<0.001	1.289	1.142–1.455	<0.001
Chemotherapy						
Yes	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
No	1.702	1.514–1.912	<0.001	1.701	1.509–1.918	<0.001

RT, radiation therapy; Ref, reference.

289 Performance status remains one of the most important  
 290 drivers of prognosis (31-34). In this population of patients  
 291 with a generally poor overall prognosis who may have been  
 292 underrepresented in the randomized trials of fractionation  
 293 for BM, it may be important to differentiate those with the  
 294 potential for longer survival as several retrospective studies  
 295 have reported associations between increased radiation dose  
 296 and improved response duration (28,35), possible improved  
 297 complete pain response rates (23,30,35), and higher  
 298 radiographic response rates (35). Since there was little  
 299 evidence for improved initial pain response, this difference  
 300 will be most important for those with the longest life  
 301 expectancy. The only randomized trial of palliative RT for  
 302 BMs from HCC showed no difference in survival or toxicity  
 303 based on the number of fractions (20–30 *vs.* 7–10 fractions),  
 304 but reported a shorter time to response with the more  
 305 hypofractionated regimen and a longer time to treatment  
 306 failure in the more fractionated group (36). Any benefits of  
 307 increased total radiation dose and longer treatment duration  
 308 need to be weighed against the potential impact on the  
 309 percent remaining life spent receiving RT and the burden  
 310 of extended radiation treatment regimens.

311 There were several limitations in this study. Like  
 312 most large database retrospective studies, the population  
 313 of patients who received 1 fraction was relatively low.  
 314 Additionally, there was no data regarding pain response,  
 315 quality of life information, retreatment, or the extent of  
 316 systemic disease at time of RT treatment, which would have  
 317 provided a more detailed analysis of response and outcomes.  
 318 The PRLSRT metric is strongly influenced by short survival  
 319 and radiation duration. Since patients in the present study  
 320 had poor survival outcomes (median survival after radiation  
 321 of about 3 months), some may question the generalizability  
 322 of the study results and the PRLSRT metric, but this  
 323 must be taken in context. It is acknowledged that several  
 324 studies of HCC patients reported longer OS outcomes with  
 325 median survival of 5–11 months (37-40), but these studies  
 326 typically calculated survival from the diagnosis of BMs  
 327 instead of the start of RT, included only 50–60% of patients  
 328 who required palliative RT, and treated patients in a more  
 329 uniform manner with high proportions receiving systemic  
 330 treatment with chemotherapy and bisphosphonates. Given  
 331 these factors, the differences in the reported survival rates  
 332 are not surprising, since it could be months between the  
 333 diagnosis of BMs and progression of the lesions to become  
 334 symptomatic enough to require intervention with radiation.  
 335 Additionally due to the rarity of the diagnosis, any center  
 336 reporting significant numbers of patients with HCC BMs

are likely centers of excellence with significant experiences  
 managing metastatic HCC, especially compared to the  
 patients in the current study, who were treated at every kind  
 of center. Despite these limitations, the current study gives  
 unique insight into the practice patterns and outcomes after  
 palliative RT for BMs from HCC and is valuable because  
 it is one of the only studies to report the survival from the  
 time of RT, which is crucial for determining prognosis and  
 radiation fractionation.

In conclusion, in this cohort of patients with BMs from  
 HCC, those who receive multifraction palliative regimens  
 have a significantly increased PRLSRT when compared  
 to single fraction RT. Despite equivalence in pain control  
 between single and multi-fraction regimens, there remains  
 a prominent underutilization of single fraction palliative  
 treatments. In the palliative treatment of painful BMs  
 from any malignancy, and particularly those with a poor  
 prognosis such as metastatic HCC, single fraction RT  
 should be utilized to reduce time spent receiving treatment  
 and the number of incomplete courses.

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 to the accuracy or integrity of any part of the work are  
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